# Predictors of neonatal encephalopathy in full term infants

Stuart J Adamson, Louisa M Alessandri, Nadia Badawi, Paul R Burton, Patrick J Pemberton, Fiona Stanley

**Abstract**

***Objective*—Preliminary investigation of the contribution of adverse antepartum and intrapartum factors to neonatal encephalopathy in singleton neonates born full term.**

***Design*—Matched case-control study based on incidence density sampling of controls.**

***Setting*—Two major teaching hospitals (one paediatric and one obstetric) and three peripheral maternity hospitals in Perth, Western Australia (population 1·2 million).**

***Subjects*—89 cases, all the full term singleton neonates born during an eight month period in 1992 who fulfilled one or more of six criteria during the first week of life (seizures, abnormal conscious state, persistent hypertonia or hypotonia, and feeding or respiratory difficulties of central origin). One full term control infant without neonatal encephalopathy was matched to each case by sex, hospital of delivery, time of day and day of the week of birth, and maternal health insurance status.**

***Main outcome measures*—Odds ratio estimates of relative risk of neonatal encephalopathy associated with antepartum and intrapartum factors.**

***Results*—Estimated incidence of moderate or severe encephalopathy in first week of life was 3·75 per 1000 full term live births. Thirteen cases and no controls had evidence suggestive of important intrapartum hypoxia, and in only five of these cases was the neurological condition at birth attributed to events during the intrapartum period. Univariate conditional logistic regression analysis identified significant differences between cases and controls for maternal vaginal bleeding in pregnancy, maternal thyroxine treatment, congenital abnormalities, induction of labour, interval from membrane rupture to delivery, maternal pyrexia in labour, augmentation of labour, abnormal intrapartum cardiotocograms, and meconium in labour. Family history of convulsions also approached significance.**

***Conclusions*—Our preliminary results suggest that intrapartum hypoxia, according to currently used criteria, was not the cause of neonatal encephalopathy in most cases in this population. Our findings suggest that many aetiologies of neonatal encephalopathy originate in the antepartum period.**

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*BMJ* 1995;311:598-602

## Introduction

Neonatal encephalopathy is an important clinical problem in infants born full term, associated with neonatal mortality and morbidity as well as unfavourable long term neurodevelopmental outcome. Neonatal encephalopathy is "a clinically defined syndrome of disturbed neurological function in the earliest days of life in the term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness, and often by seizures."[1] The reported incidence of neonatal encephalopathy ranges from one to 10 per 100 full term births.[1-6] However, most of the studies from which current estimates of incidence have been derived have dealt solely with what the authors describe as postasphyxial encephalopathy.[2-6]

The assumption that most neonatal encephalopathy is due to "intrapartum asphyxia" has served to maintain the impetus for the high level of obstetric intervention in labour,[7] but this assumption is now being questioned.[1] These interventions may have little or no influence on encephalopathy because of factors other than hypoxia but they are associated with an appreciable degree of maternal and infant morbidity.[8] This assumption also contributes to the current crisis in obstetric litigation in some countries.[9-11] The development of experimental treatments to prevent neuronal cell damage or to rescue brain cells already damaged is likely to become clinically useful in the future.[12] Because these new treatments are not free of risk they require a convincing definition of asphyxial injury.[1]

Few studies in unselected populations have examined the contribution of causes other than intrapartum hypoxia in the development of neonatal encephalopathy.[13] Our aim in this study was to identify the contribution of factors in family and maternal history, pregnancy, and birth to encephalopathic features in full term newborn infants.

## Subjects and methods

In 1992 we undertook an eight month matched case-control study of full term infants with neonatal encephalopathy in Perth, Western Australia (population 1·2 million). Cases were all singleton infants in the metropolitan area born on or after the 37th gestational week (or weighing 2500 g or more if length of gestation was unknown) and admitted to any of five study hospitals during the first week of life with a diagnosis of neonatal encephalopathy. The hospitals included two teaching hospitals (one obstetric, one paediatric) that were the only tertiary referral centres for sick neonates in Western Australia and three peripheral hospitals. The diagnosis of encephalopathy was made in the presence of at least one of the following: seizures of any type or duration; absent responsiveness to stimuli (stupor or coma); altered responsiveness (decreased or increased) to stimuli for more than 24 hours; abnormal tone for more than 24 hours; poor suck (not due to mechanical or peripheral causes) for more than 24 hours; and difficulty with control of respiration (of presumed brain stem origin), including cyanotic attacks after two days of age and recurrent apnoea at any age. Cases were ascertained by active surveillance, which included a daily cotside check of every full term baby admitted to the neonatal units at the two referral centres and at least weekly checks at the three peripheral hospitals.

One control was matched to each case and was selected from all singletons born alive on or after the 37th gestational week (or weighing 2500 g or more if length of gestation was unknown) at one of the five study hospitals and who did not have encephalopathy. Cases and controls were matched on sex, hospital of delivery, time of birth (24 hour clock), day of the week of birth, and maternal health insurance status. Exact matching was not always possible for time of day and day of the week of birth, but controls were born no later than two weeks after their corresponding case.

Informed parental consent was obtained for cases and controls, and a questionnaire was completed by the mother to ascertain maternal social, demographic, and

medical history. Retrospective antepartum and intrapartum data were collected from hospital records with a standardised recording sheet. Data items were grouped into five epochs; maternal preconceptional (13 variables); antepartum (12 variables); intrapartum (12 variables); newborn (12 variables); and neonatal (2 variables). The complete list of variables is available from the authors on request.

No reliable test is available to identify clinically important birth asphyxia.[14,15] For the purposes of this study important intrapartum hypoxia was defined as the presence of an abnormal intrapartum cardiotocograph, as interpreted by the attending clinician, or fresh meconium in labour with a one minute Apgar score of less than 3 and a five minute Apgar score of less than 6. Cases meeting these criteria were presented to two separate panels of observers, who made independent assessments of the presence of important antepartum or intrapartum factors.

Cases and controls were examined neurologically at admission and daily until discharge. By the nature of the condition it was not possible for this assessment to be carried out blind. The severity of neonatal encephalopathy among cases was graded as mild, moderate, or severe according to clinical criteria modified from Sarnat's criteria.[16] Infants with severe encephalopathy needed more than 24 hours' mechanical ventilation, required multiple anticonvulsant treatments, or were subject to coma or death. Infants with moderate encephalopathy had important neurological abnormalities or recurrent seizures requiring anticonvulsant treatment, but abnormalities resolved before discharge. Babies with subtle neurological abnormalities, including brief or single seizures, and complete resolution within the first three days were graded as having mild encephalopathy. The results of biochemical, microbiological, genetic, metabolic, imaging, and neurophysiological tests that were carried out as clinically indicated were available to help ascertain the cause of the encephalopathy.

TABLE I—*Principal entry criteria for diagnosis of 89 cases of neonatal encephalopathy*

| Criteria | No of cases |
|---|---|
| Seizures | 22 |
| Irritability or lethargy, abnormal tone and feeding | 20 |
| Irritability or lethargy and poor feeding | 11 |
| Coma or stupor | 9 |
| Respiratory problems | 8 |
| Poor feeding | 6 |
| Irritability or lethargy | 5 |
| Irritability or lethargy and abnormal tone | 5 |
| Abnormal tone | 3 |

TABLE II—*Differences of interesting magnitude between full term infants with neonatal encephalopathy and controls (univariate analysis)*

| Characteristic | No (%) of cases (n=89) | No (%) of controls (n=89) | Odds ratio (95% confidence interval) | P value |
|---|---|---|---|---|
| *Maternal preconceptional* | | | | |
| Family history of convulsions | 5/89 (6) | 0/89 | ∞ (0·94 to ∞) | 0·059* |
| *Antepartum* | | | | |
| Vaginal bleeding | 16/89 (18) | 4/89 (4) | 5·00 (1·48 to 17·27) | 0·011 |
| Thyroxine exposure | 6/89 (7) | 0/89 | ∞ (1·22 to ∞) | 0·029* |
| Congenital abnormalities | 15/89 (17) | 3/89 (3) | 5·00 (1·45 to 17·27) | 0·003 |
| *Intrapartum* | | | | |
| Induction | 40/87 (46) | 24/89 (27) | 2·33 (1·19 to 4·59) | 0·014 |
| Interval from membrane rupture to delivery (hours): | | | | |
| 0-12 | 59/81 (73) | 79/89 (89) | 3·25 (1·06 to 9·96) | 0·019 |
| 13-23 | 15/81 (19) | 8/89 (9) | 1·00 | |
| ≥24 | 7/81 (9) | 2/89 (2) | 3·50 (0·73 to 16·84) | |
| Maternal pyrexia in labour | 8/89 (9) | 0/89 | ∞(1·80 to ∞) | 0·007* |
| Augmentation of labour† | 15/86 (17) | 30/89 (34) | 0·46 (0·23 to 9·92) | 0·027 |
| Reported abnormal cardiotocograph‡ | 39/55 (71) | 14/39 (36) | 7·25 (2·55 to 20·62) | <0·001 |
| Meconium in labour | 32/83 (39) | 8/79 (10) | 11·50 (2·71 to 48·78) | <0·001 |
| Operative vaginal delivery | 31/87 (36) | 20/89 (22) | 1·92 (0·95 to 3·85) | 0·068 |
| *Newborn* | | | | |
| One minute Apgar score: | | | | |
| 0-3 | 27/87 (31) | 1/89 (1) | 64·09 (7·43 to 552·80) | <0·001 |
| 4-7 | 37/87 (43) | 29/89 (33) | 5·47 (1·87 to 16·01) | |
| 8-10 | 23/87 (26) | 59/89 (66) | 1·00 | |
| Time to first gasp ≥1 minute | 22/83 (27) | 1/88 (1) | 22·00 (2·97 to 163·22) | <0·001 |
| Time to spontaneous regular respiration (minutes): | | | | |
| <2 | 36/77 (47) | 77/89 (87) | 1·00 | <0·001 |
| 2-4 | 13/77 (17) | 6/89 (7) | 3·13 (1·09 to 9·01) | |
| ≥5 | 28/77 (36) | 6/89 (7) | 7·63 (2·58 to 22·54) | |
| Bag and mask or intubation after delivery | 41/89 (46) | 6/89 (7) | 9·75 (3·48 to 27·28) | <0·001 |
| Chemical resuscitation | 42/89 (47) | 11/89 (12) | 3·50 (1·41 to 8·67) | 0·007 |
| Gestational age (weeks): | | | | |
| 37 | 13/87 (15) | 6/89 (7) | 3·14 (0·93 to 10·56) | 0·080 |
| 38-39 | 27/87 (31) | 34/89 (38) | 1·00 | |
| 40-41 | 41/87 (47) | 47/89 (53) | 1·27 (0·63 to 2·60) | |
| ≥42 | 6/87 (7) | 2/89 (2) | 6·37 (0·66 to 61·18) | |
| Birth weight (g): | | | | |
| <3000 | 27/89 (30) | 12/89 (13) | 2·45 (1·72 to 4·91) | |
| 3000-4000 | 52/89 (58) | 71/89 (80) | 1·00 | |
| ≥4000 | 10/89 (11) | 6/89 (7) | 2·11 (0·74 to 6·04) | 0·019 |

*Fisher's exact test, 2-tailed.
†Negative relation to risk.
‡Cardiotocographs were not performed for 29 cases and 50 controls; for five cases where a cardiotocograph was performed the result was unknown.

### STATISTICAL ANALYSIS

Conditional logistic regression models,[17] each invoking a single explanatory covariate, were used in a matched analysis of the univariate relation of individual exposures with case or control status. There were a small number of rare exposures to which no controls were exposed. These were associated with infinite odds ratios, and two tailed P values were obtained by ignoring the matching and using Fisher's exact test.[18] It is unlikely that inferences based on this approach would have been seriously misleading because it is improbable that the matching variables used would have induced close correlation between the matched cases and controls for those few exposure variables analysed in this manner.

The principal purpose of this preliminary exploratory study was to generate hypotheses for subsequent definitive testing. In screening a large number of variables for potential association with case or control status we used the likelihood ratio test and, as is customary, adopted $P<0{\cdot}05$ as a formal definition of significance. However, significance alone is a poor indicator of biological or clinical relevance.[19,20] Given that it was our purpose to generate hypotheses for testing in larger definitive studies, we have therefore erred in favour of presenting all results that might potentially be of interest to others and deliberately elected not to use a multiple test procedure to make P values more conservative. Accordingly, we have presented results from all variables exhibiting a possible association with case or control status that is unlikely to have occurred by chance ($P<0{\cdot}05$ or of borderline significance) and all variables that were of clear clinical relevance a priori. Any positive findings we report should be interpreted cautiously as some of the observed associations might have arisen by chance, as might those from any analysis based on statistical significance. Furthermore, despite our inclusive philosophy, this preliminary study is relatively small, and it is possible that some real associations have remained undetected.

## Results

The study population comprised 89 cases and 89 controls. Table I shows the clinical entry criteria; the most common reason for inclusion was seizures. Of the 89 cases, 42 met our criteria for moderate or severe neonatal encephalopathy. This group represents our best estimate of moderate or severe encephalopathy in the Perth metropolitan area during the eight month study. There were about 11 200 full term deliveries during the period of study in the Perth metropolitan area. These data suggest an estimated incidence of moderate or severe neonatal encephalopathy in the first week of life of 3·75 (95% confidence interval 2·75 to 5·11) infants per 1000 full term live births.

Table II details the associations of interest between explanatory variables and case or control status. Five

cases and no controls had a mother with a history of convulsions (no mothers were taking anticonvulsant treatment). There were no other substantial associations between any other preconceptional factors and case or control status.

### ANTEPARTUM FACTORS

There were substantial differences between cases and controls for congenital abnormalities, bleeding during pregnancy, and maternal thyroxine replacement treatment. Three cases and no controls had a history of major physical trauma during pregnancy.

There were 15 congenital abnormalities in the cases, 10 major defects (two cases with inborn errors of metabolism; one case each with Alagille syndrome, VACTERL sequence, Dandy-Walker syndrome, cystic dilatation of the third ventricle and coloboma of the iris, myelomeningocoele, and partial agenesis of the corpus callosum; and two cases with Down's syndrome) and five minor defects (all multiple minor dysmorphisms). In most of the 10 cases with major defects it is likely that the encephalopathy was due to the defect. There were three major abnormalities in controls (one infant with an omphalocoele, one with asymptomatic congenital hypothyroidism, and one with congenital adrenal hyperplasia).

No substantial differences were found between cases and controls with regard to reported maternal alcohol consumption and smoking during pregnancy, pregnancy induced hypertension, gestational diabetes, preterm labour, genitourinary infections, other maternal infections, oligohydramnios or polyhydramnios, hyperemesis, or anaemia.

### INTRAPARTUM FACTORS

Substantial differences were observed between cases and controls in relation to induction of labour, augmentation of labour, interval between rupture of membranes and delivery, maternal pyrexia, reported abnormal cardiotocography, and presence of meconium (table II). The mean interval from membrane rupture to delivery for cases was 10 hours compared with 6·2 hours for controls. Maternal pyrexia occurred in eight of the cases and none of the controls.

Intrapartum cardiotocographs were performed on 55 cases but only 39 controls; this may reflect the clinicians' concern about pre-existing risk factors. Of those performed, the proportion of cases with a cardiotocograph reported as being abnormal by the attending clinician was more than double that for controls. Cases were also four times more likely than controls to have fresh meconium during labour. Among cases with moderate or severe neonatal encephalopathy, meconium was six times more frequent (18 cases *v* 3 controls). Four cases but no controls had old meconium.

Operative vaginal delivery (forceps delivery or vacuum extraction) was undertaken in 35% of cases and 22% of controls. Caesarean sections were performed on a similar proportion of cases and controls, and length of established labour (first and second stages) was similar.

### NEWBORN FACTORS

Many more cases than controls had low 1 and 5 minute Apgar scores. Cases also tended to take longer to achieve regular respiration, and 10 required ventilation from birth. There were also considerable differences between cases and controls with regard to time to first gasp, bag and mask or intubation after delivery, and pharmacological resuscitation. Cord pH was measured in 27 cases and 10 controls. Three cases had a cord pH below 7·00 (6·95, 6·78, and 6·73), as did one control (6·89).

Although the gestational age of all study participants was greater than 37 weeks, an interesting excess of cases was found at the extremes of gestation. Similarly, five cases and no controls had a birth weight less than 2500 g, and 10 cases and six controls had a birth weight greater than 4000 g. The distributions of head circumferences and crown-heel length were also more likely to be clustered about the mean in controls than in cases, although the differences were not significant. More cases than controls were small for their gestational age after correction for maternal height and parity (13 cases *v* 5 controls). Altogether 67% of the subjects were male.

Seven of the case infants died in the neonatal period, a mortality of 8%. No controls died during the neonatal period. Non-neurological morbidity was three times more common in cases than controls; the five most common morbidities in cases were metabolic disturbances (n=31); respiratory complications (n=18); jaundice (n=26); renal complications such as haematuria, proteinuria, and oliguria (n=12); and infection (n=13). Six of the 12 cases with renal complications had an obvious cause; three had congenital urinary tract anomalies, two had prolonged antepartum ischaemia, and one had a group B streptococcal infection. In controls jaundice was the most common non-neurological finding (n=24), followed by infection (n=7) and respiratory complications (n=3). There were no controls with renal complications.

### INTRAPARTUM HYPOXIA

Thirteen cases (15%) but no controls fulfilled our definition for important intrapartum hypoxia. A cord pH was recorded in seven of the cases, and two of these were low (6·73 and 6·78). Renal signs (oliguria, haematuria and proteinuria) were present in five cases; only one case had both renal morbidity and a low cord pH. Both panels of observers determined that eight of the 13 cases had an important antepartum risk factor that may have contributed to the encephalopathy (table III). However, five cases assessed by the two panels had important intrapartum factors that could have been causally associated with the neonatal encephalopathy without any known damaging antepartum event (table III).

## Discussion

This preliminary study has shown that antepartum factors may play a role in the aetiology of neonatal encephalopathy. Only 15% of the cases and no controls fulfilled our criteria suggestive of significant intrapartum hypoxia. A large proportion of these cases had a significant antepartum history, so that the intrapartum period alone was implicated in the aetiology of neonatal encephalopathy in only 6% of the cases. The findings related to family history of convulsions and maternal thyroxine exposure are consistent with other studies, are biologically plausible, and are worthy of further investigation.[21-24] Maternal vaginal bleeding in pregnancy was found to be a significant risk factor for neonatal encephalopathy in this study. An association between antepartum haemorrhage and cerebral palsy has also been shown.[25,26] We noted an excess of not only central nervous system congenital abnormalities in cases but, as with cerebral palsy,[27,28] also of multiple minor anomalies. This suggests that early prenatal factors had contributed to the neonatal encephalopathy.

Pyrexia during labour and a longer interval between membrane rupture and delivery were associated with neonatal encephalopathy. Fetal sepsis at term has been associated with a deterioration in the fetal acid-base status and a prolongation of labour,[29] while Nelson and Ellenberg have shown that prolonged rupture of

membranes and chorioamnionitis are major predictors of cerebral palsy.[30]

The results of our study suggest that the cases experienced a more adverse antepartum course than the controls. We also noted an important difference between cases and controls in measures of fetal response, such as an abnormal cardiotocograph or low Apgar scores, with little evidence to suggest major differences in other intrapartum parameters, such as duration of labour. Although the relative importance of the antepartum and the intrapartum period in terms of neonatal encephalopathy remains unclear, the previous bias for considering only intrapartum features is clearly untenable. The antepartum and intrapartum periods may be totally independent, or an important sequence leading to neonatal encephalopathy may be antepartum events followed by specific intrapartum events. Another possibility is that intrapartum events such as cardiotocograph abnormalities and meconium are, in fact, the first clinical manifestation of neonatal encephalopathy in some cases.

To unveil the various pathways of neurological

TABLE III—*Cases of neonatal encephalopathy with possible intrapartum asphyxia*

| Case No | Antepartum factors | Intrapartum factors | Others |
|---|---|---|---|
| | | *Cases with important contribution from antepartum events* | |
| 1 | Pregnancy induced hypertension | Spontaneous labour<br>Severe shoulder dystocia<br>13 minutes to deliver baby<br>Fresh meconium<br>No cardiotocograph<br>Apgar scores 0, 0, 0* | Adrenal haemorrhage<br>Haematuria<br>Large for gestational age (4980 g)<br>Neonatal death |
| 2 | Mother smoked 5-10 cigarettes a day<br>Pregnancy induced hypertension at 33 weeks<br>Placental infarctions | Spontaneous labour<br>No meconium<br>Fetal bradycardia 45 minutes before delivery<br>Apgar scores 1, 5, 6*<br>Cord pH 6·7 | |
| 2 | Pregnancy induced hypertension at term | Induced because of pregnancy induced hypertension<br>Face presentation<br>Pronounced dips and severe decelerations with no beat to beat variation; bradycardia 40 beats/min<br>No meconium<br>Apgar scores 0, 3, -* | |
| 4 | Mother smoked 20-30 cigarettes a day<br>Chorioamnionitis | Occipitoposterior, spontaneous labour<br>Wrigley's forceps<br>Fresh meconium<br>No cardiotocograph<br>Apgar scores 0, 0, 2* | Neonatal death |
| 5 | Antepartum haemorrhage at 22 weeks | Spontaneous labour, failed vacuum, forceps delivery<br>Bradycardia to 40 beats/min lasting 40 mins with decelerations<br>Fresh meconium<br>Apgar scores 1, 1, -* | Haematuria<br>Oliguria<br>Neonatal death |
| 6 | Mother smoked 10-15 cigarettes a day<br>Mother intellectual disability<br>Sibling intellectual disability<br>*Trichomonas vaginalis* infection<br>Decreased fetal movements<br>Abnormal cardiotocograms<br>Presented on numerous occasions for decreased fetal movements<br>Abdominal trauma<br>Suspicion of substance abuse<br>Calcified placenta | Induced at 40 weeks<br>Meconium<br>Baseline bradycardia<br>Apgar scores 1, 3, -*<br>Cord pH 7·37 BE +2 | Neonatal death |
| 7 | Breech<br>Failed external cephalic version 2 weeks before birth | Spontaneous labour<br>Bradycardia in second stage<br>No meconium<br>Apgar scores 1, 4, 7* | |
| 8 | Hereditary bleeding disorder<br>Crohn's disease<br>Hospitalised for threatened preterm labour at 32 weeks<br>Mild hypertension<br>Calcified placenta<br>Iris coloboma in baby | Induced for post-term and mild hypertension<br>Vacuum delivery for maternal distress and failure to progress<br>Meconium<br>No cardiotocograph<br>Apgar scores 2, 3, 10* | |
| | | *Cases with important contribution from intrapartum events* | |
| 9 | Two urinary tract infections | Spontaneous labour<br>Meconium<br>Bradycardia for 18 minutes<br>Vacuum extraction after non-elective caesarean section refused<br>Apgar scores 1, 2, 3* | Renal failure<br>Coagulopathy<br>Subgaleal bleed<br>Syndrome of inappropriate antidiuretic hormone secretion |
| 10 | Urinary tract infection at 28 weeks | Induced at 40 weeks<br>Profound prolonged maternal hypotension, baby delivered with high forceps<br>Bradycardia<br>No meconium<br>Apgar scores 1, 2, 3* | Depressed fracture left frontal bone<br>Left facial palsy |
| 11 | No abnormality detected | Spontaneous labour<br>Cord tight around the neck<br>Meconium<br>No cardiotocograph<br>Apgar scores 0, 4, 6* | Placenta showed pronounced vascular congestion probably caused by an acute intrapartum event |
| 12 | No abnormality detected | Induced for post dates<br>Forceps delivery for cord prolapse<br>Large decelerations for bradycardia for 16 minutes<br>Meconium<br>Apgar scores 1, 2, 4*<br>Cord pH 7·28 | Acute renal failure<br>Neonatal death |
| 13 | Decreased fetal movements day before delivery with non-reactive non-stress test† | Induced due to decreased fetal movements<br>Meconium staining at artificial rupture of membranes<br>Low lying placenta<br>Vasa praevia<br>Intrapartum haemorrhage of 400 ml 30 minutes before delivery by non-elective caesarean section<br>Bradycardia 70 beats/min after the antepartum haemorrhage<br>Apgar scores 1, 2, 4*<br>Cord pH 6·778 BE—15·8 | Transient acute renal failure |

*Apgar scores measured at 1, 5, and 10 minutes.
†Despite the presence of antepartum factors in this case, it is included in this group as the vasa praevia with intrapartum haemorrhage could account for the encephalopathy in its own right.

## Key messages

- Neonatal encephalopathy is an important clinical problem
- In this study the incidence of moderate or severe encephalopathy was found to be 3·75 per 1000 live term births, with a case fatality of almost 8%
- Intrapartum hypoxia, determined with traditional criteria, was not the cause of neonatal encephalopathy in most cases
- Signs of intrapartum fetal distress may be the first signs of pre-existing neurological abnormality, and events occurring in the antepartum period are an important cause of neurological abnormality in newborn infants
- These results have implications for obstetricians, paediatricians, and legal practitioners

insult that lead to neonatal encephalopathy we therefore need (*a*) more specific markers of intrapartum insult than those currently used, (*b*) better antepartum and preconceptional history to reduce the problem of non-random missing data and unknown exposures, (*c*) a reliable assessment of the state of the fetus and its reserve towards the end of the antepartum period before starting labour, and (*d*) larger population based studies that may be analysed with methodologies such as path analysis[31] so that hypotheses based on complex causal chains can be investigated.

We thank staff in the study hospitals and all metropolitan and regional paediatricians for their cooperation. In particular we thank Dr Peter Silberstein (neurologist at Princess Margaret Hospital); Drs Ronnie Hagan, Noel French, Alfred Grauaug, and Jeff Tompkins (neonatologists at King Edward Memorial Hospital); and Drs Rick Christie and Aida Partridge for their important contributions to the clinical aspect of this study. We also thank Drs Eve Blair and Jenny Kurinczuk for reviewing the paper, Ms Carol Garfield for help with the computing and figures, and Ms Helen Howells for help with typing.

Funding: SJA was supported by a Raine Foundation Scholarship.

Conflict of interest: None.

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*(Accepted 13 June 1995)*

# Consequences of occupational asthma

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*BMJ* 1995;311:602-3

Some 500 new cases of occupational asthma are reported annually in the United Kingdom, a figure considered to underestimate the true incidence by at least threefold[1]; most patients are young and economically active. Previous studies of the socioeconomic outcomes of occupational asthma have not distinguished the consequences of developing asthma from those specific to occupational asthma.[2,3]

## Patients, methods, and results

We surveyed all patients referred to a specialist clinic between 1987 and 1992 who had been given a final diagnosis of asthma. All had been referred for investigation of a possible occupational cause; most had subsequently been discharged. Using the clinician's final diagnosis, patients were divided into three categories: those with occupationally induced asthma, those with pre-existing or coexisting asthma exacerbated by work, and those with asthma unrelated to work. Diagnoses were made by a combination of clinical history, measurement of specific antibodies, serial peak flow recordings, and specific inhalation testing. A postal questionnaire inquired into job changes made because of asthma, consequences on income, difficulties in acquiring new work, and current treatment. Socioeconomic group was recorded by using a standard classification.[4]

We surveyed 225 subjects: 113 (50%) had occupational asthma, 37 (16%) had asthma exacerbated by work, and 75 (33%) has asthma unrelated to work. These proportions did not change over the five years,